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High Dose Chemotherapy (HDCT) with Autologous Stem Cell Transplantation (ASCT) in Children with Solid and Central Nervous System (CNS) Tumors, a Single Centre Experience

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Abstract

Objective: The Primary aim of this study is to assess the outcome of children with solid and CNS tumors who underwent HDCT and ASCT at King Fahad Specialist Hospital in Dammam, secondarily we aim to compare our local results with national and international outcomes, Identify the toxicities, and complications of this modality of treatment, and identify the outcome in term of overall survival and relapse and mortality rates.

Design: This is a retrospective cross-sectional study of all the pediatric patients below sixteen-year-old who diagnosed with solid tumor or central nervous system tumor and treated by high dose chemotherapy and autologous stem cell transplantation in king Fahd specialist hospital in Dammam, pediatric hematology/ oncology department between 1st November 2011 and 29th February 2020, our study included 33 cases.

Setting: It is a single center study at King Fahad Specialist Hospital in Dammam which is 400 beds tertiary referral hospital with 27 beds pediatric oncology Ward, 4 beds bone marrow transplant and 18 bed pediatric oncology day care services.

Methods and Results: After obtaining the IRB approval, all data and information of patients were retrieved from patients' hard files and electronic medical records. Data analysis were done by using Statistical Package for the Social Sciences (SPSS) program version and stored in the Redcap system for confidentiality.

Results: Within our study period we diagnosed 33 cases who diagnosed with solid tumor or central nervous system malignancies and treated by high dose chemotherapy and autologous stem cell transplantation in king Fahd specialist hospital in Dammam, the overall survival was 66% with both the relapse rate and mortality rate were 33%.

Conclusion: In summary, despite being a single-center experience and relatively small sample size, yet we believe that our study showed that the approach of using HDCT followed by APBSCT for managing children with advanced malignant solid tumors is safe and effective with the best results obtained in those with complete remission status before that approach. A prospective study will be more suitable to evaluate whether HDCT with auto-PBSCT will significantly impact the outcomes in the treatment of children with advanced malignant solid tumors. a serious international collaboration is crucial to design randomized trials aiming to address these expensive and high morbidity procedures in treating childhood advanced solid malignant tumors.

Keywords: High Dose Chemotherapy (HDCT) • Autologous Stem Cell Transplantation (ASCT) • Children with solid tumors • Central Nervous System (CNS) Tumors •Tandem stem cell transplantation • Advanced solid tumors

Introduction

Despite the development of new treatment options, that including improving the surgical abilities to respect the solid tumors as much as it could be approached, combination of more than one chemotherapeutic agent in addition to radiation therapy provision and biological immunotherapy, yet, the prognosis of high-risk patients with advance local or metastatic solid and central nervous system tumors are still poor with about the half of patients experience disease progression with high disease related fatalities in general [1]. The trials to intensify the consolidation therapy with autologous stem-cell rescue after myeloablative doses of chemotherapy have been showed to improve the survival for some group of children, with no advantage for Allo-HSCT can be detected in the EBMT data for any pediatric solid tumors indication. For more than a decade this approach was used in neuroblastoma, and it has subsequently been tried to nearly to all types of childhood solid tumors' [2]. however, it is so hard to tell the exact conclusions on the advantages of this approach when compared to non- myeloablative treatment regimens, probably because of the paucity of pediatric patients that are transplant candidates, the wide range of solid tumors that are treated by different protocols, and the disease status at the time of myeloablation [3], but the available data so far showing that with the exception of metastatic neuroblastoma there is still no proven role for this treatment approach [2].

However, recent data showed some promising results for the high-dose chemotherapy as a first line therapy in other high-risk children's solid tumors such as MB [4], yet there still no clear role or significant benefit in other types of high-risk solid tumors as in pediatric metastatic rhabdomyosarcoma [5]. The EBMT registry data stated that there is a clear evidence for the advantage of HDT/auto-HSCT with an increasing interest in tandem transplants in neuroblastoma and Ewing sarcoma while in the other pediatric solid tumors, indication still lacks randomized trials [6-8]. In this study we present our single center experience over about 8 years period with the approach of myeloablative chemotherapy followed by ASCT for young patients with aggressive solid tumors.

Material and Methods

The outcomes of 33 children with high risk malignant solid and central nervous system tumors, who were treated with high-dose chemotherapy and

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autologous peripheral blood stem cell transplantation in king Fahd specialist hospital in Dammam, pediatric hematology/ oncology department, between 1st November 2011 and 29th February 2020 were retrospectively analyzed. After obtaining the IRB approval (HAME 0318), required data extracted from patient's electronic medical records then computerized using Microsoft Excel sheet and revised instantaneously. Computerized data will be exported to SPSS (Statistical Package for Social Sciencesver.25). Frequency tables were drawn to explore the findings (frequencies, percentages, measures of central tendencies and dispersion and graphics).

Cross-tabulation and ANOV (analysis of variance) used to explore the magnitude of diagnostic interval and the most significant factors affecting it and percentages. Overall survival and event free survival were illustrated by the Kaplan Meier curves. Data stored in Redcap system for confidentiality.

Results

We studied the clinical characteristics of 33 patients (19 boys and 14 girls) who met the inclusion criteria. The two major groups were the neuroblastoma and the medulloblastoma patients which involved about 88% of our study cases. Twenty-two (66.6%) patients had neuroblastoma, seven (21.2%) had medulloblastoma, and one patient (3%) for each of the following diagnosis of ATRT, germ cell tumor, medulloepithelioma and renal clear cell sarcoma (Table 1). The median age at the time of initial diagnosis was 30 months, with the youngest patient of 6 months who diagnosed with ATRT and the eldest age of 120 month who was a case of renal clear cell sarcoma. The approach of high dose chemotherapy followed by autologous stem cell transplant was used as part of the front line on 97% of the patients while it was given as salvage therapy to 3% (one patient only who is the case of renal clear cell sarcoma).

Data of the Neuroblastoma Group

Our data of the twenty-two neuroblastoma patients (Table 2) showed that the majority of them around 77% (17 cases) were in partial remission only at the time before the transplantation, while around 18% (4 cases) were in complete remission status pre transplant, and only 1% (1 case) had stable disease status. All the cases of neuroblastoma in this study were given single HDC/ASCT without immune therapy, since the approach of tandem transplantation with immune therapy was adopted after our study period in our Centre. The extent of tumor resection was classified as complete resection (95-100%), gross total resection (90-95%), incomplete resection (50–90%), and biopsy (<50%). Patients were then stratified based on the International Neuroblastoma Risk Group (INRG) staging system (17). Two of the 4 cases who were in complete remission underwent complete surgical resections for all the tumor sites at the time of control surgery but near total resection could only be done for the other two cases. Fortunately, all of them were free of disease after HDC/ASCT until the time of reporting (Table 3). On the other hand, for the group of 17 cases who had partial remission, complete surgical resection was done only in 4 patients and 7 cases had near total resection while the rest of 6 could offered only some debulking surgeries, unfortunately around 41% of theses group had disease recurrence within the first 2 year after the transplantation and died because of that, while one extra death happened in that group as well due to transplant related mortality of severe pulmonary hypertension (Table 3). The single case who had stable disease status and underwent debulking surgery, fortunately went into remission after HDC/ASCT and maintained his remission till the time of publication. With regard to the N-myc status of the neuroblastoma cases around 40% of the total cases were N-myc positive, in relation to the subcategories we had 75% (three out of the 4 patients) of the complete remission group where N-myc negative, while nearly half of the partial remission group (52%) where N-myc negative, in addition to also negative N-myc status to the single patient in the stable disease group (Table 2).

Data of the Medulloblastoma Group

For the medulloblastoma group data (Table 4) we got 7 patients in this study, four out of them where in complete remission and gross total resection was possible in three of them while the other one case had near total resection, and all of them were in good remission and free of disease after HDC/ASCT (Table 5). The other 3 cases of medulloblastoma showed partial remission status with near total resection done in 2 of them and one had only debulking, that one is the only one who experience relapse and died (Table 5).

For each patient belongs to the other group of ATRT, germ cell tumor and renal clear cell sarcoma unfortunately all of them experience disease recurrence and died later except the case of the renal clear cell sarcoma who was referred abroad for trial therapy. The stem cell source from all the patients was obtained from peripheral collection from the blood with C34 dose range between 3.8 to 16.4 × 106 /kg, the average days to engraftment was 12.6 to neutrophils and 14 to platelets. The conditioning therapy (Table 6) that used as myeloablative is similar to that used in other childhood cancer treating centers.

Table 1: Patients Diagnosis Frequencies and Percentages (N=33).

Diagnosis	Frequency (f)	Percentage (%)
ATRT	1	3
Germ cell tumor	1	3
Medulloblastoma	7	21.2
Medulloepithelioma	1	3
Neuroblastoma	22	66.7
Renal clear cell sarcoma	1	3
Total	33	100

Table 2: Neuroblastoma Patients' Data (N=22).

Category	Sub-Category	Control Surgery Type	N-MYC Status (+ve) / (-Ve) *	Frequency (f)	Percentage (%)
Remission Status After Induction	Complete Remission (4)18.2%	Complete Surgery	Both (-ve)	2	9.1
		Near Total Surgery	1(+ve), 1(-ve)	2	9.1
	Partial Remission (17)77.3%	Complete Surgery	1(+ve), 3(-ve)	4	18.2
		Near Total Surgery	4(+ve), 3(-ve)	7	31.8
		Debulking Surgery	3(+ve), 3(-ve)	6	27.3
	Stable Disease (1)4.5%	Debulking Surgery	1(-ve)	1	4.5
Total				22	100
* (+ve) Positive, (-ve) Negative					

Table 3: Neuroblastoma Survival Outcome Patients' Data.

Category	Sub-Category	Survival Outcome	Frequency (f)	Percentage (%)
Remission Status After Induction	Complete Remission (4)18.2%	Alive and in Remission	4	100
	Partial Remission (17)77.3%	Alive and in Remission	9	52.9
		Relapsed and Died	7	41.2
		Transplantation-Related Death	1	5.9
	Stable Disease (1)4.5%	Alive and in Remission	1	100

Table 4: Medulloblastoma Patients' Data (N=7).

Category	Sub-Category	Control Surgery Type	Chemotherapy Protocol	Frequency (f)	Percentage (%)
Remission Status After Induction	Complete Remission (4)57.2%	GTR	ACNS0334	2	28.6
			ACNS0334		
		NTR	ACNS 0334	2	28.6
			CCG99703		
	Partial Remission (3)42.8%	Near Total Surgery	ACNS 0334	2	28.6
			CCG99703		
		Debulking Surgery	Medulloblastoma GPHO	1	14.3
Total				7	100

Table 5: Medulloblastoma Survival Outcome Patients' Data (N=7).

Category	Sub-Category	Survival Outcome	Frequency (f)	Percentage (%)
Remission Status After Induction	Complete Remission (4)57.2%	Alive and in Remission	4	100
		Alive and in Remission	2	66.6
	Partial Remission (3)42.8%	Relapse and Died	1	33.3

Table 6: Conditioning Regimens Used as Myeloablative.

Conditioning Regimen	Category
Brain tumors	Carboplatin-Thiotepa
Germ cell tumor	Melphalan-Thiotepa
Neuroblastoma	Busulphan-Melphalan
Renal clear cell sarcoma	Busulphan-Melphalan

Table 7: Complication Post HDT/ASCT.

Complication	Frequency (f)	Percentage (%)
Oral Mucositis	27	82
Nausea and Vomiting	25	76
Fever	16	48
Bacteremia	10	30
CMV Viremia	7	21
Pulmonary Fungal Infection	2	6
Abnormal Liver Function	2	6
VOD	1	3
Pulmonary Hypertension	1	3
Septic Shock	2	6
Emergent Hypertension	1	3

Radiation therapy was given to the patients according to their protocol guidelines.

The most common seen complication (Table 7) was GIT toxicity in form of oral mucositis in about 82%, nausea and vomiting in 76%. Fever was documented in 16 cases (48%), 10 (30%) patients had positive bacteremia in their blood cultures, another 7 cases (21%) had CMV viremia, and 2 (6%) cases diagnosed with fungal infection. Liver function was impaired mildly in 2 cases (6%), only one case developed Veno-Occlusive disease of the Liver (VOD) and another one case developed severe respiratory distress and pulmonary hypertension and died because of that. Serious complications occurred in 4 patients (12%) necessitating admission to pediatric intensive care unit as 2 (6%) cases developed septic shock and one case had emergent hypertension and also that case who developed severe respiratory distress and pulmonary hypertension and died later on in PICU.

The average days of hospitalization for all the cases was around 33 days. Regarding the disease recurrence data, we got 11 (33%) patients experienced disease relapse after HDC/ASCT and their distribution per disease type as shown in (Table 8): Unfortunately,10 out of those who experienced disease recurrence passed away and one case referred abroad for trial therapies, and he was alive at a time of reporting. One extra death as mentioned earlier occurred due to transplantation related complications in form of severe pulmonary hypertension, that case was given bleomycin and melphalan in his conditioning therapy. So, both the relapse (Figure 1) and the mortality rate were similar in this study about 33% with overall survival about 66% (Figure 2).

Table 8: Relapse Distribution among Diseases (N=11).

Diagnosis	Frequency (f)	Percentage (%)
Neuroblastoma	7	63.6
Medulloblastoma	1	9.1
ATRT	1	9.1
Germ Cell Tumor	1	9.1
Renal Clear Cell Sarcoma	1	9.1
Total	11	100

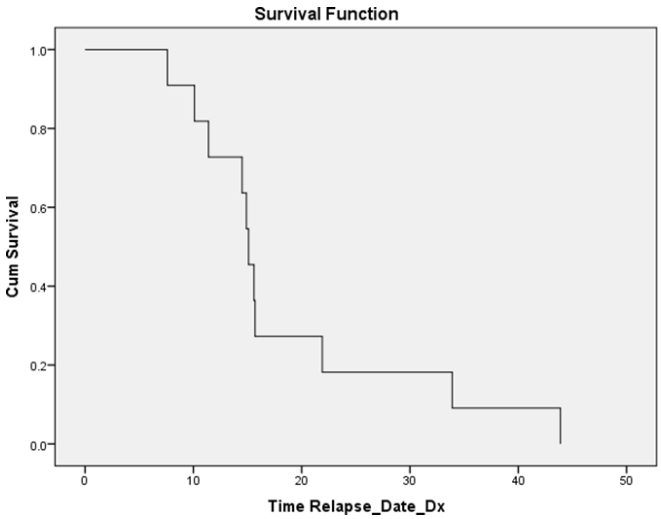

Figure 1. Relapse Function.

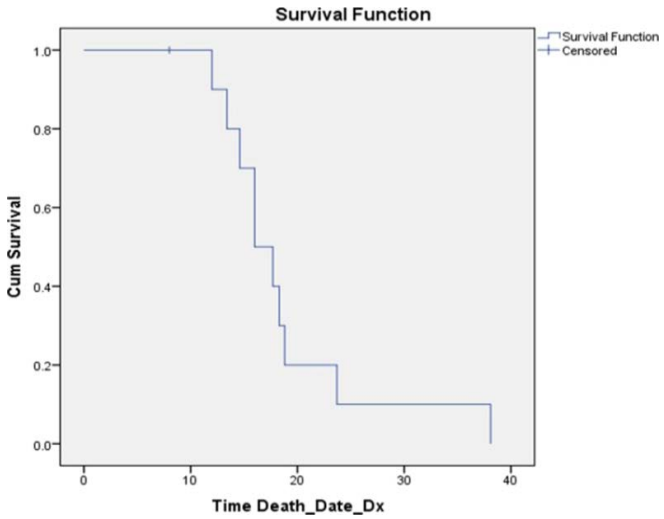

Figure 2. Survival function.

Discussion

Fortunately, the rapid progress in the development of new chemotherapy agents, targeted therapies, increased availability of stem cell transplantation from different donor's types, improved supportive care, and successful intensification of therapy for high-risk and very-high-risk patients with Acute lymphoblastic leukemia have improved outcomes in the past decade and promise to cure even more children in the coming decade [6]. However, on the other hand, the management of advanced/relapsed solid tumors is still considered a major challenge in paediatric oncology with only limited improvements have been made in their outcome. In 2006 Ceschel et al. in a large multicenter cohort study [7] reported the 10-year OS and event-free survival of children with relapsed solid tumors as 33% and 27%, respectively. Since then, more and more trials and studies conducted on those groups of paediatric patients with relapsed/progressed solid tumors intending to improve their prognosis. There lies the significance of our study- an 8-year, single-centre study that served as the only referring centre to treat childhood cancer in the eastern province in Saudi Arabia. Age had a significant impact on the outcome predictions. The youngest does usually better than adolescent age who is generally associated with inferior outcomes [8]. Definition of favorable age varies between different tumor types, while age <10 years is a favourable factor in sarcomas (Ewing tumors and rhabdomyosarcoma), neuroblastoma has a much earlier cut-off at 18 months. Patients with neuroblastoma ≤18 months at diagnosis need biological profiling and are only eligible with high-risk biological features, in particular, MYCN amplification [9]. The median age of our study population was 30 months. Patients offered the high-dose chemotherapy followed with autologous BMT as first-line proved to have a much better outcome than after disease recurrence [10]. Perentesis J et al. reported that in his study of autologous stem cell transplantation for high- risk pediatric solid tumors, the estimated 4-year survival for patients receiving a transplant while in high-risk remission was 78% In contrast, 13/15 (86%) patients that were transplanted while in partial remission died because of progressive disease or transplant-related complications. in that study, they recommended that autologous stem cell transplantation should be considered for consolidation therapy of high risk and relapsed paediatric patients with solid tumors who have achieved complete remission

Response to induction treatments prior to HDT/HSCT is critical in all indications. A short summary is CR > VGPR/PR > SR/MR > NR (SD) > RR/UR [CR complete response, VGPR very good partial response, PR partial response (>50%), SR sensitive relapse = >50% response, MR minor response (<50%), NR no response, SD stable disease, RR/UR resistant or untreated relapse (<50% response)] [8]. In our study, we found that the disease status at transplant and the extent to perform complete surgical resection prior to ASCT were identified as important prognostic factors in OS, DFS, and risk of relapse. Almost all of our relapse cases were in only partial remission and incomplete surgery.

The matter of Single versus tandem HDCT/auto-SCT is addressed in some studies with the attempt to identify the best chances of cure for the group of high risk solid or relapsed tumors in one study done on Children with Brain Tumors by Ki Woong Sung et al. They discussed that after single HDCT/auto-SCT it is very likely that the treatment failure will be due to relapse or tumor progression rather than treatment-related mortality (TRM) [11-13]. Based on that many investigators have explored the concept of tandem HDCT/auto-SCT to further improve the outcome.

This strategy depends on the hypothesis that further dose escalation might improve the survival rates. and they concluded from that study that tandem HDCT/auto-SCT might improve survival outcomes in patients with relapsed or high-risk brain tumors. In a similar study by Park et al. done in 2016 [11]. They found that the tandem myeloablative consolidation therapy improves survival rate in patients with high-risk neuroblastoma, especially when combined with post-consolidative immunotherapy.

In this study, around 80% of the cases had a single ASCT (including the neuroblastoma group) while only 20% had tandem BMT. despite that our overall survival was about 66%, probably the value of our overall survival was overestimated than what is mentioned in the literature for those group of patients. It might be due to the short follow up time from the end of the study to the time of publication and further re-evaluation of the survival rate in future could adjust the figures. However, the best conditioning regimen has not yet been established. High-dose chemotherapy regimens should consist of one or several agents that have dose-response-related anti-cancer activity and do not have overlapping extra-haematological toxicities [14].

Busulfan-melphalan: This HDT combination is the only one in the EBMT database resulting in significantly improved survival rates in neuroblastoma and Ewing tumors [8]. This issue was addressed in a similar study by J Hara et al. [15], from Japan when their study showed that the double-conditioning regimens consisting of thiotepa, melphalan, and busulfan with stem cell rescue for the treatment of paediatric solid tumors can be given safely at nearly maximum doses with less toxicity than single-cycle regimens of drug administration. The major toxicity was mucositis. these regimens resulted in a good response in advanced paediatric malignancies, especially in patients Double-conditioning regimens patients in the out centre followed different preparative regimen's as shown on the result without significant toxic manifestations apart from one patient who was given bleomycin and melphalan and died of severe pulmonary hypertension the most reported complications to the HDC /ASCT in our patients were the Gastrointestinal tract toxicity with a high incidence of oral mucositis and nausea and vomiting, similar results from WEI-LING ZHANG et al. in which they reported that all their 37 cases (100%) developed different degrees of oral ulceration, vomiting, diarrhoea in comparison to 82% mucositis incidence and 76% nausea and vomiting in our research.

Similarly, we reported a rate of 30% of bacteraemia post-HDC/ASCT, which is near to what was published by Paola Perez, et al, from Colombia [16] that the percentage of patients who developed at least one episode of bacteraemia was (41.4%), in the paediatric patients with hematopoietic stem cell transplantation (HSCT).

Our data showed a relapse rate of 33% of our cases which is going along with the data of Ceschel et al., [7] in a large multicentred cohort study published in 2006, in which he reported the 10-year OS and event-free survival of children with relapsed solid tumors as 33% and 27%, respectively. In this study the event-free survival could not be estimated accurately due to the shoer follow up period from end of the study till publication time. With an overall survival rate of 66% which is higher than what is reported in the literature but as we explained earlier this percentage may be overestimated due to the shoer follow up period from the end of the study to the time of publication

Conclusion

In summary, despite being a single-centre experience and relatively small sample size, yet we believe that our study showed that the approach of using HDCT followed by APBSCT for managing children with advanced malignant solid tumors is safe and effective with the best results obtained in those with complete remission status before that approach.

We thought that the Survival rates in our study might be overestimated due to the short follow up period at the time of reporting of this study, and definitely more time is needed to analyse the final outcome and assess the long-term toxicities for using the HDCT followed by APBSCT. A prospective study will be more suitable to evaluate whether HDCT with auto-PBSCT will significantly impact the outcomes in the treatment of children with advanced malignant solid tumors. A serious international collaboration is crucial to design randomized trials to address these expensive and high morbidity procedures in treating childhood advanced solid malignant tumors. Especial attention to the targeted agents and cancer immunotherapies should be given as they may become the mainstay of future therapies.

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